

EP1384477

Publication Title:

UTILIZATION OF PYRAZOLINE DERIVATIVES IN THE PREPARATION OF A
MEDICAMENT FOR THE PREVENTION AND/OR TREATMENT OF
PROLIFERATIVE CELL DISEASES

Abstract:

Abstract of EP1384477

Derivatives of pyrazoline (I), wherein R1 is hydrogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, carboxylic acid, alkyl carboxylate with 1 to 4 carbon atoms, carboxamide or cyano, R2 is hydrogen or methyl, R3, R4, R7 and R8, independently are hydrogen, chlorine, fluorine, methyl, trifluoromethyl or methoxy, R5 and R6, independently, are hydrogen, chlorine, fluorine, methyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylaminosulphonyl, with the condition that one of the substituents R5 or R6 is a methylsulphonyl, aminosulphonyl or acetylaminosulphonyl group, and with the condition that when R1 is methyl, then R2 is hydrogen or methyl, R3 and R8, independently are hydrogen, chlorine, fluorine, methyl, or trifluoromethyl, R4 is hydrogen, fluorine, methyl, trifluoromethyl or methoxy, R5 is fluorine, trifluoromethyl, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylaminosulphonyl, R6 is hydrogen, chlorine, fluorine, methyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylaminosulphonyl, with the condition that one of the substituents R5 or R6 is a methylsulphonyl, aminosulphonyl or acetylaminosulphonyl group, and R7 represents an atom of hydrogen, chlorine, fluorine, a methyl, trifluoromethyl or methoxy group; useful for preventing or treating cell proliferation diseases. <chem> Data supplied from the esp@cenet database - Worldwide

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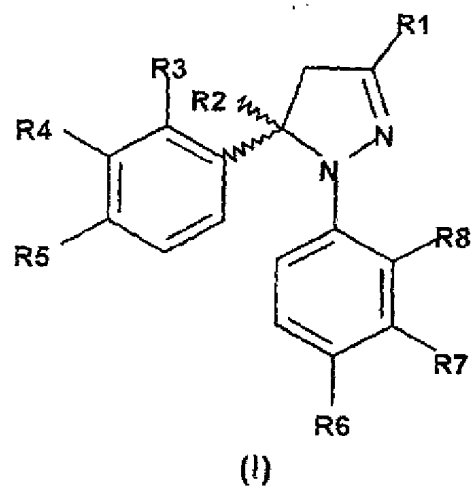
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(54) **UTILIZATION OF PYRAZOLINE DERIVATIVES IN THE PREPARATION OF A MEDICAMENT
FOR THE PREVENTION AND/OR TREATMENT OF PROLIFERATIVE CELL DISEASES**

(57) Derivatives of pyrazoline (I), wherein R_1 is hydrogen, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, carboxylic acid, alkyl carboxylate with 1 to 4 carbon atoms, carboxamide or cyano, R_2 is hydrogen or methyl, R_3 , R_4 , R_7 and R_8 , independently are hydrogen, chlorine, fluorine, methyl, trifluoromethyl or methoxy, R_5 and R_6 , independently, are hydrogen, chlorine, fluorine, methyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylaminosulphonyl, with the condition that one of the substituents R_5 or R_6 is a methylsulphonyl, aminosulphonyl or acetylaminosulphonyl group, and with the condition that when R_1 is methyl, then R_2 is hydrogen or methyl, R_3 and R_8 , independently are hydrogen, chlorine, fluorine, methyl, or trifluoromethyl, R_4 is hydrogen, , fluorine, methyl, trifluoromethyl or methoxy, R_5 is fluorine, trifluoromethyl, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylaminosulphonyl, R_6 is hydrogen, chlorine, fluorine, methyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylaminosulphonyl, with the condition that one of the substituents R_5 or R_6 is a methylsulphonyl, aminosulphonyl or acetylaminosulphonyl group, and R_7 represents an atom of hydrogen, chlorine, fluorine, a methyl, trifluoromethyl or methoxy group; useful for preventing or treating cell proliferation diseases.

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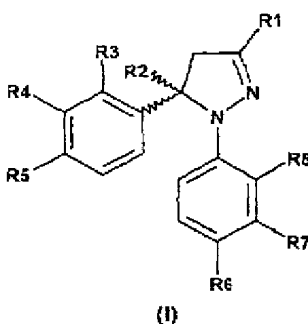
Description

Field of the Invention

[0001] The present invention relates to the use of pyrazoline derivatives with the general formula (I), as well as their physiologically acceptable salts, in the preparation of medicament useful in human and/or veterinary therapy for preventing or treating cell proliferation diseases, particularly for treatment of preneoplastic or neoplastic processes, tumoral angiogenesis, cachexia and processes related to tumoral necrosis factor (TNF) and in general any processes that can benefit from inhibiting the expression of the gene responsible for synthesis of cyclooxygenase-2 (COX-2), whether alone or in combination with other products, producing a synergy in the latter case.

Background of the Invention

[0002] Our patent application number WO 99/62884 describes compounds with general formula (I) and their physiologically acceptable salts.



As inhibitors of the enzyme cyclooxygenase-2 (COX-2), with application in Medicine as anti-inflammatories.

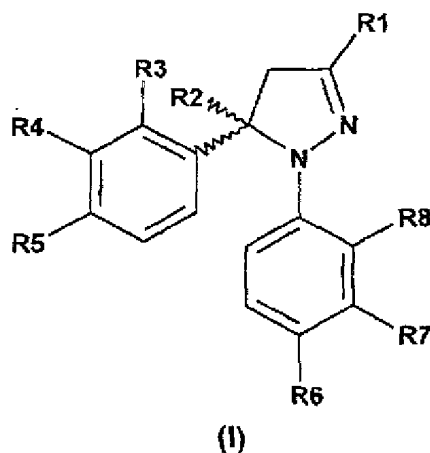
[0003] The growing interest in the regulation of the gene responsible for synthesis of COX-2 derives from its application not only in its anti-inflammatory response but also in important pathological processes, such as cell proliferation and cancer, regulation of the immune response, degenerative diseases of the brain, etc., as made manifest in the growing related literature. A set of observations has led to considering COX-2 inhibitors as potential chemopreventive agents in colorectal cancer (CRC). The choice of COX-2 as a target is based on the frequency of its over-expression: up to 90% of carcinomas and 40% of adenomas of the colon show high amounts of mRNA and protein of COX-2 (Eberhart et al. : *Gastroenterology* 1994 107 : 1183-1188; Du Bois et al. : *Gastroenterology* 1996 110: 1259-1262; Prescott et al., *Cell* 1996 87: 783-786). In addition, it seems clear that this over-expression contributes to the tumoral phenotype in CRC: a) overexpression of COX-2 has been related to inhibition of apoptosis (Tsujii et al: *Cell* 1995 83: 493-501); b) inactivation of COX-2 in Apc (-) mice is associated with inhibited tumoral growth; c) two of the most common gene alterations in colorectal cancer, mutations in the Apc tumour suppression genes and mutations in ras oncogenes are related to the overexpression of COX-2 (Boolbol et al: *Cancer Res.* 1996 56: 2556-2560; Sheng H. et al: *J. Biol. Chem.* 1998 273 (34): 2120-2127).

[0004] Our patent application PCT/ES00/00245 describes a cell line comprised of a DNA construct consisting of all or part of a promoter sequence for the COX-2 gene and a token gene, operatively connected to each other so that said promoter sequence for the COX-2 gene directs the expression of said token gene in response to a suitable stimulus. The test method involves placing in contact said cell line with the compound to be tested and determining the existence of a signal indicating the expression of activity due to the token gene. This method is claimed as suitable for searching for selective inhibitors of the induction at a transcription level of COX-2 by suitable stimuli.

[0005] We have now found that the compounds of general formula (I), as well as their physiologically acceptable salts, are especially useful for preparing medicament of use in human and/or veterinary therapy for prevention or treatment of cell proliferation diseases, particularly for treatment of preneoplastic or neoplastic processes, angiogenesis, cachexia and processes related to tumoral necrosis factor (TNF) and, in general, processes which can benefit from inhibition of expression of the gene responsible for synthesising cyclooxygenase2 (COX-2), whether alone or in combination with other products, in which case a synergy occurs.

Detailed Description of the Invention

[0006] The present invention relates to the use of pyrazoline derived of Δ^2 -pyrazoline, also known as 4,5-dihydro-1*H*-pyrazols, of general formula (I)



in the preparation of a medicament of use in human and/or veterinary therapy for prevention or treatment of cell proliferation diseases, particularly for the treatment of preneoplastic or neoplastic processes, angiogenesis, cachexia and processes related to tumoral necrosis factor (TNF) and, in general, processes which can benefit from inhibition of expression of the gene responsible for synthesising cyclooxygenase2 (COX-2), whether alone or in combination with other products, in which case a synergy occurs.

[0007] In the formula (I)

R_1 represents an atom of hydrogen, a methyl, fluoromethyl, difluoromethyl, trifluoromethyl, carboxylic acid, alkyl carboxylate with less than 1 to 4 carbon atoms, carboxamide or cyano group,

R_2 represents an atom of hydrogen or a methyl group,

R_3 , R_4 , R_7 and R_8 , like or different, represent an atom of hydrogen, chlorine, fluorine, a methyl, trifluoromethyl or methoxy group,

R_5 represents an atom of hydrogen, chlorine, fluorine, a methyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylaminosulphonyl group

R_6 represents an atom of hydrogen, chlorine, fluorine, a methyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylaminosulphonyl group,

with the condition that one of the substituents R_5 or R_6 is a methylsulphonyl, aminosulphonyl or acetylaminosulphonyl group, and

with the condition that when R_1 represents a methyl group

R_2 represents an atom of hydrogen or a methyl group,

R_3 and R_8 , like or different, represent an atom of hydrogen, chlorine, fluorine, a methyl or trifluoromethyl group,

R_4 represents an atom of hydrogen, fluorine, a methyl, trifluoro-methyl or methoxy group,

R_5 represents an atom of fluorine, a trifluoromethyl, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylaminosulphonyl group,

R_6 represents an atom of hydrogen, chlorine, fluorine, a methyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylaminosulphonyl group,

with the condition that one of the substituents R_5 or R_6 is a methylsulphonyl, aminosulphonyl or acetylaminosulphonyl group, and

R_7 represents an atom of hydrogen, chlorine, fluorine, a methyl, trifluoromethyl or methoxy group.

[0008] The compounds with the general formula (I) have a stereogenic centre and thus can be prepared enantiomerically pure or as racemates. The racemates of compounds (I) can be resolved into their optical isomers by conventional methods, such as by chiral separation chromatography or by fractional crystallisation of their diastereoisomeric salts, which can be obtained by reacting the compounds (I) with enantiomerically pure acids or bases. Likewise, it they can also be obtained by enantioselective synthesis using enantiomerically pure chiral precursors.

[0009] The present invention also relates to the physiologically acceptable salts of the compounds with general

formula (I), to the mineral and organic acid addition salts and to those formed with alkali metals.

[0010] The compounds with general formula (I), as well as their physiologically acceptable salts, inhibit the expression of the gene responsible for synthesis of cyclooxygenase-2 (COX-2) as can be shown with a cell system of stable transfectant JURKAT cells with the promoter of the gene COX-2 associated to the gene for luciferase, according to the method described in our patent application PCT/ES00/00245.

[0011] The compounds with general formula (I) can be used, administering a therapeutically effective dose, in mammals, including man, as agents for prevention or treatment of preneoplastic or neoplastic processes, partially or totally inhibiting the growth, propagation or metastasis of the neoplasia, as well as the partial or total destruction of neoplastic cells. For example, the compounds with general formula (I) can be used in neoplasias such as gastrointestinal cancer, liver cancer, bladder cancer, pancreatic cancer, lung cancer, prostate cancer, ovarian cancer, cervical cancer and breast cancer, or for prevention or treatment of adenomatose polyps including familial polyposis.

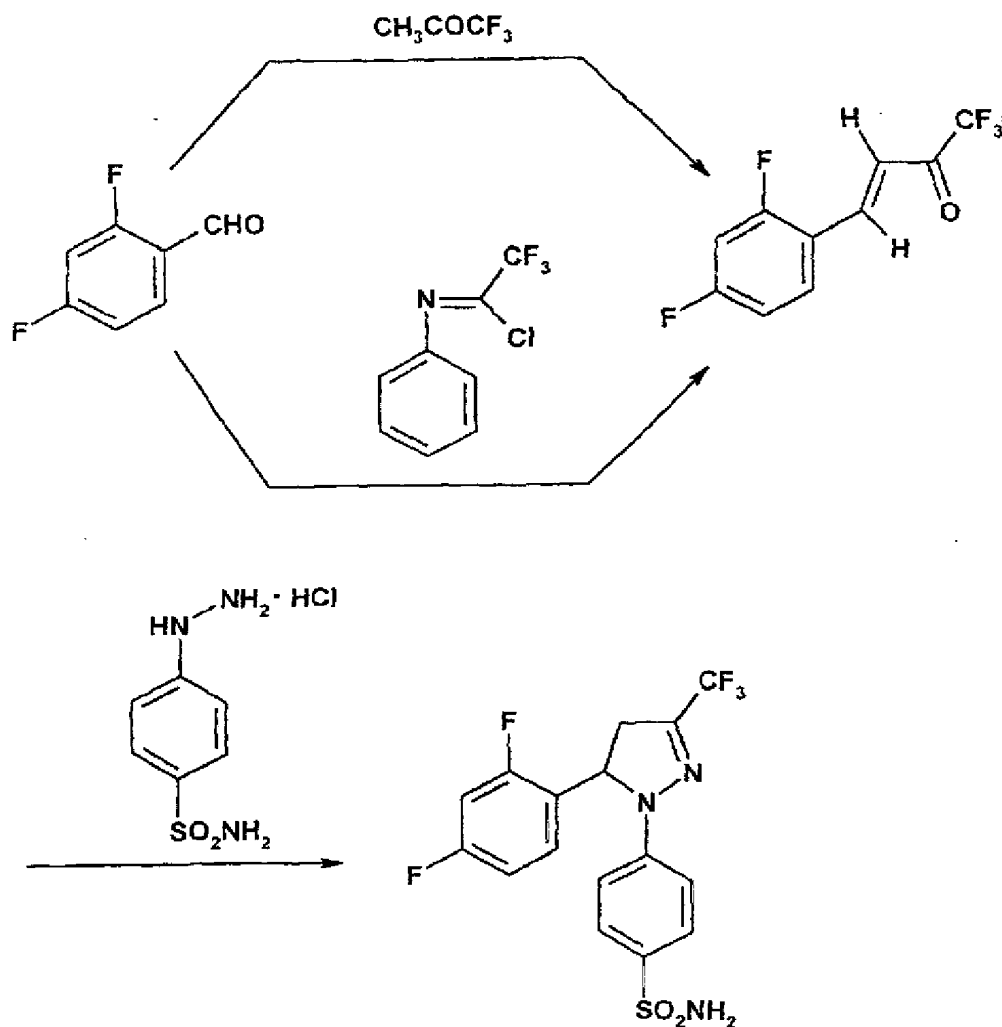
[0012] The compounds with general formula (I) can be used, administering a therapeutically effective dose, in mammals, including man, as agents for prevention or treatment of diseases related to angiogenesis, such as tumoral growth and metastasis that rely on an angiogenic process, and in other disorders such as retinopathies and endometriosis.

[0013] The compounds with general formula (I) can be used, administering a therapeutically effective dose, in mammals, including man, as agents for prevention or treatment of cachexia and other disorders in which the tumoral necrosis factor- α (TNF- α) is involved.

[0014] The derivatives of general formula (I) can be prepared according to the methods described in our patent application WO 99/62884. Below is described, by way of example, the preparation of 1-(4-aminosulphonylphenyl)-5-(2,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol (Example 3) and its enantiomers (Examples 79 and 80). Tables 1 and 2 show a family of compounds of particular interest which respond to the general formula (I), as well as their characterising physical-chemical properties.

Example 3. - Preparation of 1-(4-aminosulphonylphenyl)-5-(2,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol

[0015]



Preparation, via acetylmidoyl, of (E)-1,1,1-trifluoro-4-(2,4-difluorophenyl)-3-buten-2-one

[0016] In a flask with a dry inert atmosphere are introduced 260 ml of anhydrous THF, it is cooled to -78°C and 225 ml are added of LDA 2M solution in THF/n-heptane at a rate allowing to maintain the temperature under -65°C . After this diethylmethylphosphonate (34.25 g, 0.225 mol) is quickly added dropwise dissolved in 30 ml of THF and it is shaken for 30 minutes at -78°C . N-phenyltrifluoroacetylmidoyl chloride is then added dropwise (46.7 g, 0.225 mol) dissolved in 40 ml of THF and it is left with shaking in the same conditions for 1 hour. A solution is added of 2,4-difluorobenzaldehyde (33.6 g, 0.236 mol) in 40 ml of THF, the cold bath is removed and the temperature is allowed to rise to ambient temperature. It is left shaking overnight in these conditions. The following morning 450 ml of HCl 2N are added and the shaking continued for 24 hours. The THF is removed in the rotovapor and the resulting aqueous solution is extracted with AcOEt (2x200 ml), washed with a solution of 5% NaHCO_3 and with a saturated NaCl solution, it is dried with sodium sulphate, filtered and the solvent evaporated with the rotovapor. In this way are obtained 54.6 g of a reddish liquid crude that solidifies. The crude is distilled at a pressure of 35 mbar and a fraction is collected of (E)-1,1,1-trifluoro-4-(2,4-difluorophenyl)-3-buten-2-one at $107-14^\circ\text{C}$ (43 g, 81%). Melting point : $50-1^\circ\text{C}$

IR (KBr, cm^{-1}) : 1717, 1602, 1583, 1277, 1146, 1059, 706

^1H -RMN (CDCl_3) : 6,9 (m, 2H), 7.05 (d, $J=16$ Hz, 1H), 7,6 (m, 1H), 8.0 (d, $J=16$ Hz, 1H)

¹³C-RMN (CDCl₃): 105.1 (t, J=26Hz), 112.6(dd, J=4, 22Hz), 116.4 (q, J=291Hz), 118.2, 118.5, 131.5 (dd, J=4, 11Hz), 141.5, 162.5 (dd, J=13, 193Hz), 165.7 (dd, J=13, 190Hz), 180 (q, J=36Hz)

Preparation via aldolic condensation of (E)-1,1,1-trifluoro-4-(2,4-difluorophenyl)-3-buten-2-one

[0017] In a flask are dissolved 2,4-difluorobenzaldehyde (250 g, 1.76 mol), glacial acetic acid (152.5 g, 2.54 mol) and piperidine (152.5 g, 1.79 mol) in 3 l of THF. The solution is cooled to 5-10°C and CF₃COCH₃ (≈140 g, 1.2 mol) is bubbled through it. The cold bath is removed, the temperature is allowed to rise to ambient temperature and it is left with shaking at said temperature for 2 hours. CF₃COCH₃ (≈40 g, 0.36 mol) is added once again and left shaking for 2 hours. Another ≈40 g are added and shaken for another 2 hours, and so on until a total of about 415 g (3.7 mol) of CF₃COCH₃ have been added. Ammonium chloride 20% solution (600 ml) is added and the solvent is eliminated at a low pressure (50°C, 80 mbar). 300 ml of water are added and extracted with AcOEt. The organic phase is washed with water, H₂SO₄ 5%, water and dried over anhydrous sodium sulphate. It is filtered and evaporated. The resulting crude is distilled, to collect (30 mbar) a fraction (281.4 g, 68%) of (E)-1,1,1-trifluoro-4-(2,4-difluorophenyl)-3-buten-2-one with melting point 50-1°C. IR, ¹H-RMN and ¹³C-RMN identical to the product obtained via acetylmoyl.

Preparation of 1-(4-aminosulphonylphenyl)-5-(2,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol

[0018] A solution of 4-(aminosulphonyl)phenylhydrazine chlorhydrate (243.8 g, 1.09 mol) and (E)-1,1,1-trifluoro-4-(2,4-difluorophenyl)-3-buten-2-one (281.4 g) in 1600 ml of acetic acid is refluxed for 24 hours in a nitrogen atmosphere. It is cooled, poured slowly over water-ice (10-12 l) while vigorously shaken and filtered. It is washed with toluene (500 ml) and dried. 328 g of crude product are obtained (purity: 95.6%) which crystallises from dioxane. 216.7 g are obtained of 1-(4-aminosulphonylphenyl)-5-(2,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol with a purity of 98.1%. The crystallisation liquor, once concentrated, provide a further 69.3 g with 97.5% purity. The union of these two fractions is recrystallised from isopropanol, yielding 267.8 g (61%) of ground product with a particle size < 100 µm, purity of 99.5% and melting point 161-2°C

Elementary analysis	% C	%H	%N	%F
Calculated	47.41	2.98	10.37	23.43
Obtained	47.42	2.77	10.35	23.57
IR (KBr, cm ⁻¹)	3315, 3232, 1617, 1593, 1506, 1326, 1179, 1099, 1067			

¹H-RMN [300 MHz, CDCl₃, 25°C, δ (ppm)]: 3.0 (dd, J=6.3 and 11.4 Hz, 1H); 3.80 (dd, J=11.4 and 12.6 Hz, 1H); 4.79 (s wide, 2H); 5.70 (dd, J=6.3 and 12.6 Hz, 1H); 6.8-6.95 (m, 2H); 7.01-7.09 (m, 3H); 7.74 (d, J=8.7 Hz, 2H)

¹H RMN [300 MHz, DMSO-d₆, 25°C, δ (ppm)]: 3.13 (dd, J=18, 5 Hz, 1H); 3.89 (t, J=16 Hz, 1H); 5.96 (dd, J=13, 6 Hz, 1H); 7.03-7.16 (m, 5H); 7.33 (m, 2H); 7.64 (d, J=9 Hz, 2H)

¹³C-RMN [75 MHz, CDCl₃, 25°C, δ (ppm)]: 40.2, 57.9, 104.9 (t, J=25Hz), 112.4 (dd, J=4, 22Hz), 113.5, 120.4 (q, J=269Hz), 122.1 (d, J=17Hz), 128, 128.2, 133.5, 139.5 (q, J=38Hz), 145.8, 159.6 (dd, J=12, 245Hz), 163 (dd, J=12, 248Hz)

¹³C RMN [75 MHz, DMSO-d₆, 25°C, δ (ppm)]: 39.7, 58.8, 105.1 (t, J^{C-F}=26 Hz), 112.1 (dd, J^{C-F}=22, 3 Hz), 113.3, 120.9 (q, J^{C-F}=268 Hz), 123.1 (dd, J^{C-F}=14, 4 Hz), 127.4, 130.0 (dd, J^{C-F}=10, 5 Hz), 135.9, 139.0 (q, J^{C-F}=37 Hz), 144.6, 160.0 (dd, J^{C-F}=247, 13 Hz), 162.3 (dd, J^{C-F}=246, 13 Hz)

MS [EI, -70 eV, m/z (%): 405 (M⁺, 100), 386 (4), 341 (7), 292 (14), 156 (26), 139 (16)

Preparation of (+)-1-(4-aminosulphonylphenyl)-5-(2,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol

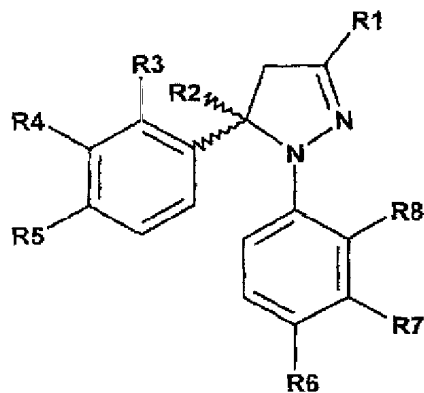
(Example 79) and (-)-1-(4-aminosulphonylphenyl)-5-(2,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol

(Example 80)

[0019] The racemic mixture (±)-1-(4-aminosulphonylphenyl)-5-(2,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol is resolved into its enantiomers by high resolution liquid chromatography using a CHIRALPAK AS column with particle size 10 µ and dimensions 25 × 2 cm (Daicel), mobile phase 0.1% of diethylamine in methanol and flow rate of 8 ml/min. With a retention time of 7.4 minutes (+)-1-(4-aminosulphonylphenyl)-5-(2,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol is obtained as a white solid with m.p.: 173-4°C; enantiomeric purity 99.9 %; [α]_D=+183.9 (c=1 CH₃OH). With a retention time of 9.2 minutes (-)-1-(4-aminosulphonylphenyl)-5-(2,4-difluorophenyl)-

4,5-dihydro-3-trifluoromethyl-1*H*-pyrazol is obtained as a white solid with m.p.: 173-4°C; enantiomeric purity >99,9%; $[\alpha]_D = -189.4$ ($c=1$ CH₃OH).

Table 1



Example	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈
1	CF ₃	H	H	H	CH ₃	SO ₂ NH ₂	H	H
2	CF ₃	CH ₃	H	H	H	SO ₂ NH ₂	H	H
3	CF ₃	H	F	H	F	SO ₂ NH ₂	H	H
4	CF ₃	H	H	H	SO ₂ CH ₃	CH ₃	H	H
5	CF ₃	H	H	H	H	SO ₂ NH ₂	H	H
6	CF ₃	H	H	H	H	SO ₂ CH ₃	H	H
7	CF ₃	H	H	H	CH ₃	SO ₂ CH ₃	H	H
8	CF ₃	H	H	H	F	SO ₂ NH ₂	H	H
9	CF ₃	H	H	H	F	SO ₂ CH ₃	H	H
10	CF ₃	H	H	H	SO ₂ CH ₃	F	H	H
11	CF ₃	H	H	F	F	SO ₂ NH ₂	H	H
12	CF ₃	H	Cl	H	Cl	SO ₂ CH ₃	H	H
13	CF ₃	H	Cl	H	Cl	SO ₂ NH ₂	H	H
14	CF ₃	H	CH ₃	H	H	SO ₂ NH ₂	H	H
15	CF ₃	H	H	CH ₃	H	SO ₂ NH ₂	H	H
16	CF ₃	H	F	H	H	SO ₂ NH ₂	H	H
17	CF ₃	H	F	H	H	SO ₂ CH ₃	H	H
18	CF ₃	H	H	F	H	SO ₂ NH ₂	H	H
19	CF ₃	H	H	F	H	SO ₂ CH ₃	H	H
20	CF ₃	H	H	H	OCH ₃	SO ₂ NH ₂	H	H
21	CF ₃	H	H	Cl	F	SO ₂ NH ₂	H	H
22	CF ₃	H	H	H	OCF ₃	SO ₂ NH ₂	H	H
23	CF ₃	H	F	F	H	SO ₂ NH ₂	H	H
24	CF ₃	H	CH ₃	H	CH ₃	SO ₂ NH ₂	H	H
25	CF ₃	H	H	F	F	SO ₂ CH ₃	H	H
26	CH ₃	H	H	H	F	SO ₂ NH ₂	H	H
27	CH ₃	H	H	H	F	SO ₂ CH ₃	H	H

28	CH ₃	H	H	H	CH ₃	SO ₂ NH ₂	H	F
29	CH ₃	H	H	H	CH ₃	SO ₂ CH ₃	H	H
30	CH ₃	H	H	H	CF ₃	SO ₂ NH ₂	H	H
31	H	H	H	H	H	SO ₂ NH ₂	H	H
32	H	H	H	H	H	SO ₂ CH ₃	H	H
33	CH ₃	H	H	H	CF ₃	SO ₂ CH ₃	H	H
34	CO ₂ H	H	H	H	CH ₃	SO ₂ NH ₂	H	H
35	CO ₂ H	H	H	H	H	SO ₂ NH ₂	H	H
36	CO ₂ H	H	H	H	CH ₃	SO ₂ CH ₃	H	H
37	CO ₂ CH ₃	H	H	H	CH ₃	SO ₂ NH ₂	H	H
38	CO ₂ CH ₃	H	H	H	H	SO ₂ NH ₂	H	H
39	CO ₂ CH ₃	H	H	H	CH ₃	SO ₂ CH ₃	H	H
40	CONH ₂	H	H	H	H	SO ₂ NH ₂	H	H
41	CONH ₂	H	H	H	CH ₃	SO ₂ NH ₂	H	H
42	CONH ₂	H	H	H	CH ₃	SO ₂ CH ₃	H	H
43	CN	H	H	H	CH ₃	SO ₂ CH ₃	H	H
44	CF ₃	H	H	CH ₃	CH ₃	SO ₂ NH ₂	H	H
45	CF ₃	H	H	CH ₃	OCH ₃	SO ₂ NH ₂	H	H
46	CF ₃	H	H	F	OCH ₃	SO ₂ NH ₂	H	H
47	CF ₃	H	F	H	OCH ₃	SO ₂ NH ₂	H	H
48	CF ₃	H	OCH ₃	H	OCH ₃	SO ₂ NH ₂	H	H
49	CF ₃	H	OCH ₃	H	F	SO ₂ NH ₂	H	H
50	CHF ₂	H	CH ₃	H	CH ₃	SO ₂ NH ₂	H	H
51	CF ₃	H	F	F	F	SO ₂ NH ₂	H	H
52	CF ₃	H	Cl	H	F	SO ₂ NH ₂	H	H
53	CF ₃	H	F	H	CF ₃	SO ₂ NH ₂	H	H
54	CF ₃	H	CF ₃	H	CF ₃	SO ₂ NH ₂	H	H
55	CF ₃	H	CH ₃	F	H	SO ₂ NH ₂	H	H

56	CF ₃	H	CH ₃	H	OCH ₃	SO ₂ NH ₂	H	H
57	CHF ₂	H	F	H	F	SO ₂ NH ₂	H	H
58	CF ₃	H	CF ₃	H	F	SO ₂ NH ₂	H	H
59	CF ₃	H	H	H	SO ₂ CH ₃	F	H	F
60	CF ₃	H	Cl	H	H	SO ₂ NH ₂	H	H
61	CF ₃	H	F	H	Cl	SO ₂ NH ₂	H	H
62	CF ₃	H	CH ₃	H	F	SO ₂ NH ₂	H	H
63	CF ₃	H	F	H	CH ₃	SO ₂ NH ₂	H	H
64	CF ₃	H	F	H	F	SO ₂ NHCOCH ₃	H	H
65	CF ₃	H	H	H	SO ₂ CH ₃	Cl	H	H
66	CF ₃	H	H	H	SO ₂ CH ₃	H	H	H
67	CF ₃	H	H	H	SO ₂ CH ₃	H	H	F
68	CF ₃	H	H	H	SO ₂ CH ₃	Cl	H	CH ₃
69	CF ₃	H	H	H	SO ₂ CH ₃	H	F	H
70	CF ₃	H	H	H	SO ₂ CH ₃	H	CH ₃	H
71	CF ₃	H	H	H	SO ₂ CH ₃	CH ₃	H	CH ₃
72	CF ₃	H	H	H	SO ₂ CH ₃	H	H	Cl
73	CF ₃	H	H	H	SO ₂ CH ₃	H	H	CH ₃
74	CF ₃	H	H	H	SO ₂ CH ₃	Cl	H	Cl
75	CF ₃	H	H	H	SO ₂ CH ₃	H	H	CF ₃
76	CF ₃	H	H	H	SO ₂ NH ₂	F	H	H
77	CH ₃	H	H	H	SO ₂ CH ₃	H	H	H
78	H	H	H	H	SO ₂ CH ₃	F	H	H

Exam-ple	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈	Enantiomeric Purity %	Specific Rotation [α] _D
79	CF ₃	H	F	H	F	SO ₂ NH ₂	H	H	>99	+183, 9 (c=1; CH ₃ OH)
80	CF ₃	H	F	H	F	SO ₂ NH ₂	H	H	>99	-189.4 (c=1; CH ₃ OH)
81	CF ₃	H	H	H	SO ₂ CH ₃	F	H	H	>99	+181.2 (c=1; CH ₃ OH)
82	CF ₃	H	H	H	SO ₂ CH ₃	F	H	H	>99	-183.4 (c=1; CH ₃ OH)
83	CF ₃	H	H	H	SO ₂ CH ₃	F	H	F	>99	+88 (c=1; CH ₃ OH)
84	CF ₃	H	H	H	SO ₂ CH ₃	F	H	F	>99	-86 (c=1; CH ₃ OH)

Table 2

Examp le	m. p. °C	IR (KBr) cm ⁻¹	¹ H-RMN (CDCl ₃) δ ppm
1	140-3	3358, 3268, 1594, 1326, 1170, 1139, 1120, 1097	2.34(s,3H); 3(dd, J=6.9, 14Hz,1H); 3.7(dd, J=12.6, 14Hz,1H); 4.7(bs,2H); 5.4(dd, J=6.9, 12.6Hz,1H); 7.1(2d, J=8.1, 9.3Hz, 4H); 7.2(d,J=8.1Hz,2H); 7.7(d,J=9.3Hz,2H)
2	60-6	3384, 3266, 1593, 1498, 1327, 1151, 1099, 703	1.6(s,3H); 2.8(m,1H); 3.1(m,1H); 4.5(bs, 2H) ; 7.2 (m, 3H) ; 7.4-7.55(m, 4H); 7.7(d, 2H)
3	160-2	3315, 3232, 1617, 1593, 1506, 1326, 1179, 1099, 1067	3(dd,J=6.3, 11.4Hz,1H); 3.8(dd,J=11.4, 12.6Hz, 1H); 4.8(bs,2H); 5.7(dd,J=6.3, 12.6Hz,1H); 6.8-6.95(m,2H); 7-7.1(m,3H); 7.7(d,J=8.7Hz,2H)
4	140-3	1516, 1310, 1148, 1131, 1060, 774	2.2(s,3H); 2.9(dd,J=7.8, 17.1Hz,1H); 3(s, 3H); 3.7(dd,J=12.9, 17.1Hz,1H); 5.45(dd, J=7.8, 12.9Hz,1H); 6.8(d,J=8.4Hz,2H); 7(d, J=8.4Hz, 2H); 7.45(d,J=8.4Hz,2H); 7.9(d, J=8.4Hz,2H)
5	156-7	3350,3269, 1596,1315 1188, 1142,1101	3.04(dd, J=6.6, 18Hz,1H); 3.7(cd, J=12.9, 18 Hz,1H); 4.8(s,2H); 5.45(dd,J=6.6, 12,9Hz,1H); 7.0(d, J=9Hz,2H); 7.2(d, J=6.6Hz,2H); 7.3(m,3H); 7.7(d,J=9Hz,2H)

Table 2 (continued)

Examp le	m. p. °C	IR (KBr) cm ⁻¹	¹ H-RMN (CDCl ₃) δ ppm
5 6	137-40	1595, 1333, 1297, 1282, 1148, 771	3.0(s,3H); 3.06(dd,J=6.6, 18Hz,1H); 3.75 (dd, J=12.8, 18.1H); 5.45(dd,J=6.6, 12.6Hz, 1H); 7.05(d,J=9Hz,2H); 7.2(d,J=7.8Hz,2H); 7.4(m,3H); 7.7(d,J=9Hz,2H)
10 7	115-19	1592, 1332, 1148, 1133, 825, 775	2.3(s,3H); 3.0(s,3H); 3.05(dd,J=6.6, 19Hz, 1H) 3,7(dd,J=12.6, 19.1H); 5.4(dd,J=6.6, 12.6 Hz,1H); 7.1(2d,J=8.1, 8.7Hz,4H); 7.2 (d,J=8.1 Hz,2H); 7.7(d,J=8.7Hz,2H)
15 8	154-6	3337, 3254, 1594, 1510, 1324, 1158, 740	3.0(dd,J=6.6, 18Hz,1H); 3.7(dd,J=12.6, 18Hz, 1H); 4.8(s,2H); 5.4(dd,J=6.6, 12.6Hz, 1H); 7.1(m,4H); 7.2(m,2H); 7.7(d,J=9Hz, 2H)
20 9	121-22	1592, 1509, 1148, 1120, 774	3.0(s,3H); 3.05(dd,J=6.6, 17.4Hz,1H); 3.7 (dd, J=12.6, 17.4Hz,1H); 5.4(dd,J=6.6 y 12.6Hz, 1H); 7.0(m,4H); 7.2(m,2H); 7.7(d, J=9Hz,2H)
25 10	103-5	1514, 1313, 1155, 1133, 1061, 827	2.9(dd,J=8.4, 17.4Hz,1H); 3(s,3H); 3.7(dd, J= 12.6, 17.4Hz,1H); 5.4(dd,J=8.4, 12.6Hz, 1H); 6.9(m,4H); 7.45(d,J=8.4Hz,2H); 7.95 (d,J=8.4 Hz,2H)
30 11	153-5	3318, 3250, 1596, 1323, 1135, 1066	3(dd,J=6.9 y 18Hz,1H); 3.7(dd, J=12.6.18Hz, 1H); 4.7(s ancho,2H); 5.4(dd, J=6.9, 12.6Hz, 1H); 7.0(m,4H); 7.2(m, 1H); 7.7(d,J=9Hz,2H)
35 12	198-200	1596, 1320, 1303, 1138, 775	2.9-3.0(dd+s,4H); 3.85(dd,J=12.6, 18,3Hz, 1H) 5.8(dd,J=6.6, 12.6Hz,1H); 7.0(2d, J=9Hz, 3H) ; 7.2(d,J=9Hz,1H); 7.5(s,1H); 7.8(d,J=9Hz,2H)
40 13	143-5	3425, 3275, 1594, 1332, 1158, 1111, 825	2.95.(dd,J=6.3, 18.3Hz,1H); 3.8(dd,J=12.3, 18,3Hz ,1H); 4.8(s,2H); 5.8(dd,J=6.3, 12.3Hz,1H); 7.0(2d,3H); 7.2(d,J=8.7Hz,1H); 7.5(s,1H); 7.7(d,J=8.1Hz,2H)
45 14	124-6	3370, 3240, 1595, 1331, 1154, 1103	(d ₆ -DMSO), 2.4(s,3H);2.9(dd,J=6.3, 18Hz, 1H); 3.9(dd,J=13.2, 18Hz,1H); 5.9(dd, J=6.3, 13.2Hz 1H); 6.8(s ancho,1H); 7.0(d, J=9Hz,2H); 7.1 (m,3H); 7.2(t,1H); 7.25(d, 1H); 7.6(d,J=9Hz,2H)
50 15	125-8	3370, 3265, 1595, 1329, 1158, 1066	(d ₆ -DMSO), 2.3(s,3H); 3(dd,J=6.3, 18.3Hz, 1H) 3.9(dd,J=12.6, 18.3Hz,1H); 5.7(dd, J=6.3, 12.6Hz,1H); 7-7.15(m,5H); 7.25(t, 1H); 7.6(d,J=9Hz,2H)
55 16	166-8	3330, 3239, 1597, 1334, 1122, 769	3.05(dd,J=6.3, 17.7Hz,1H); 3.7(dd,J=12.6, 17.7Hz,1H); 5.7(dd,J=6.3, 12.6Hz,1H); 7-7.2(m,5H); 7.3(m,1H); 7.7(d,J=9Hz,2H)
17	117-121	1594, 1304, 1150, 1119, 776	3(s,3H);3.05(dd,J=6.6, 17.1Hz,1H); 3.8(dd, J= 12.9, 17.1Hz,1H); 5.75 (dd, J=6.6, 12,9Hz,1H); 7-7.2(m,5H); 7.3(m,1H); 7.75 (d,J=9Hz,2H)

Table 2 (continued)

Examp le	m. p. °C	IR (KBr) cm ⁻¹	¹ H-RMN (CDCl ₃) δ ppm
18	132-3	3323, 3249, 1596, 1323, 1179, 1131, 741	3(dd, J=7.2, 16.8Hz, 1H); 3.75(dd, J=12.9, 16.8Hz, 1H); 4.8(s ancho, 2H); 5.4(dd, J=7.2, 12.9Hz, 1H); 6.9(d, J=9Hz, 1H); 7.05(m, 4H); 7.4(m, 1H); 7.7(d, J=9Hz, 2H)
19	149-151	1593, 1296, 1144, 965, 789	3(s+dd, 4H); 3.75(dd, J=12.6, 13.8Hz, 1H); 5.4(dd, J=6.9, 12.6Hz, 1H); 6.9-7.1(m, 5H); 7.4(m, 1H); 7.7(d, J=9Hz, 2H)
20	125-8	3336, 3254, 1593, 1329, 1156, 1112, 834	3(dd, J=6.6, 18Hz, 1H); 3.7(s+dd, 4H); 4.75(s ancho, 2H); 5.4(dd, J=6.6, 12.9Hz, 1H); 6.9(d, J=8.4Hz, 2H); 7.05(d, J=8.4Hz, 2H); 7.1(d, J=8.4Hz, 2H); 7.7(d, J=8.4Hz, 2H)
21	171-3	3376, 3239, 1593, 1500, 1328, 1153	3(dd, J=6.9, 18.3Hz, 1H); 3.75(dd, J=12.6, 18.3Hz, 1H); 4.7(s ancho, 2H); 5.4(dd, J=6.9, 12.6Hz, 1H); 7-7.2(m, 4H); 7.3(m, 1H); 7.7(d, J=8.7Hz, 2H)
22	134-7	3386, 3265, 1595, 1259, 1159	(d ₆ -DMSO): 3(dd, J=6, 18.3Hz, 1H); 3.9(dd, J=12.9, 18.3Hz, 1H); 5.9(dd, J=6, 12.9Hz, 1H); 7.05(d, J=8.7Hz, 2H); 7.1(s ancho, 2H); 7.4(s, 4H); 7.6(d, J=8.7Hz, 2H)
23	152-4	3334, 3237, 1595, 1331, 1128, 831	3.05(dd, J=6.6, 18.6Hz, 1H); 3.8(dd, J=12.9, 18.6Hz, 1H); 4.7(s ancho, 2H); 5.7(dd, J=6.6, 12.9Hz, 1H); 6.8(m, 1H); 7-7.2(m, 4H); 7.7(d, J=7.8Hz, 2H)
24	158-160	3361, 3270, 1593, 1325, 1168, 1140, 821	2.3(s, 3H); 2.4(s, 3H); 2.9(dd, J=6.9, 17.7Hz, 1H); 3.8(dd, J=12.9, 17.7Hz, 1H); 4.7(b s, 2H); 5.6(dd, J=6.9, 12.9Hz, 1H); 6.8-7.0(m, 4H); 7.1(s, 1H); 7.7(d, J=8.4Hz, 2H)
25	132-5	1595, 1325, 1281, 1135, 774	3(s+dd, 4H); 3.8(dd, J=6.6, 18Hz, 1H); 5.45(dd, J=12.6, 18Hz, 1H); 6.9-7.05(m, 4H); 7.2(m, 1H); 7.75(d, J=9Hz, 2H)
26	206-8	3329, 3215, 1593, 1509, 1333, 1155, 817	(d ₆ -DMSO): 2(s, 3H); 2.65(dd, J=5.6, 20Hz, 1H); 3.55(dd, J=12.6, 20Hz, 1H); 5.35(dd, J=5.6, 12.6Hz, 1H); 6.8(d, J=8.4Hz, 2H); 6.95(s, 2H); 7.1-7.25(m, 4H); 7.5(d, J=8.4Hz, 2H)
27	120-3	1590, 1508, 1293, 1141	2.1(s, 3H); 2.7(dd, J=6, 18.3Hz, 1H); 2.95(s, 3H); 3.5(dd, J=12, 18.3Hz, 1H); 5.1(dd, J=6, 12Hz, 1H); 6.9(d, J=9Hz, 2H); 7(m, 2H); 7.2(m, 2H); 7.6(d, J=9Hz, 2H)
28	195-7	3300, 3210, 1594, 1509, 1330, 1157	(d ₄ -CH ₃ OH): 2(s, 3H); 2.2(s, 3H); 2.6(dd, J=5.4, 17.7Hz, 1H); 3.5(dd, J=11.7, 17.7Hz, 1H); 5.3(dd, J=5.4, 11.7Hz, 1H); 6.8(d, J=8.7Hz, 2H); 6.9(s, 2H); 7.1(m, 4H); 7.5(d, J=8.7Hz, 2H)
29	113-7	1592, 1509, 1298, 1142, 771	2.1(s, 3H); 2.3(s, 3H); 2.7(dd, J=6.3, 20Hz, 1H); 2.95(s, 3H); 3.5(dd, J=13, 20Hz, 1H); 5.1(dd, J=6.3, 13Hz, 1H); 6.9(d, J=9Hz, 2H); 7.1(m, 4H); 7.6(d, J=9Hz, 2H)

Table 2 (continued)

Examp le	m. p. °C	IR (KBr) cm ⁻¹	¹ H-RMN (CDCl ₃) δ ppm
5 30	190-4	3344, 3263, 1596, 1329, 1155, 616	(d ₄ -CH ₃ OH): 2.9(dd, J=6, 18.3Hz, 1H); 3.7 (dd, J=12, 18.3Hz, 1H); 5.3(dd, J=6, 12Hz, 1H); 7.1(m, 3H); 7.4(m, 5H); 7.7(d, J=8.7Hz, 2H)
10 31	206-8	1595, 1290, 1144, 774	2.9(s+dd, 4H); 3.6(dd, J=12.3, 18.3Hz, 1H); 5.1(dd, J=6.3, 12.3Hz, 1H); 6.9(s, 1H); 7(d, J=9Hz, 2H); 7.3(m, 6H); 7.7(d, J=9Hz, 2H)
15 32	197-202	3320, 3250, 1594, 1325, 1165	(d ₆ -DMSO): 2(s, 3H); 2.7(dd, J=5.4, 18Hz, 1H); 3.6(dd, J=12, 18Hz, 1H); 5.5(dd, J=5.4, 12Hz, 1H); 6.85(d, J=8.1Hz, 2H); 7(s, 2H); 7.4 (d, J=8, 1 Hz, 2H); 7.5(d, J=8.1Hz, 2H); 7.7(d, J=8.1Hz, 2H)
20 33	136-8	1595, 1512, 1325, 1141, 771	2.1(s, 3H); 2.7(dd, J=6.3, 19Hz, 1H); 3(s, 3H); 3.5(dd, J=12.6, 19Hz, 1H); 5.2(dd, J=6.3, 12.6Hz, 1H); 6.9(d, J=8.4Hz, 2H); 7.35(d, J=8.4Hz, 2H);
25 34	172-6	3304, 3237, 1706, 1326, 1138,	(d ₄ -CH ₃ OH): 2.35(s, 3H); 3.05(dd, J=6.6, 18.6Hz, 1H); 3.8(dd, J=12.6, 18.6Hz, 1H); 5.5 (dd, J=6.6, 12.6Hz, 1H); 7.2(m, 6H); 7.7(d, J=9Hz, 2H)
30 35	157-164	3247, 1700, 1595, 1333, 1150, 1098	(d ₄ -CH ₃ OH): 3.1(dd, J=6, 18.3Hz, 1H); 3.9 (dd, J=12.6, 18.3Hz, 1H); 5.7(dd, J=6, 12.6Hz, 1H); 7.2-7.5(m, 7H); 7.7(d, J=8.7Hz, 2H)
35 36	202-5	1730, 1582, 1275, 1206, 1134, 1087	(d ₆ -DMSO): 2.2(s, 3H); 2.8(dd, J=6.3, 18Hz, 1H); 3.05(s, 3H); 3.8(dd, J=12.6, 18Hz, 1H); 5.7 (dd, J=6.3, 12.6Hz, 1H); 7.2(m, 6H); 7.7 (d, J=9Hz, 2H); 13.2(b s, 1H)
40 37	192-7	3306, 3231, 1706, 1324, 1158	2.2(s, 3H); 3(dd, J=6.3, 18Hz, 1H); 3.2 (b s, 2H); 3.65(dd, J=12.6, 18Hz, 1H); 3.8(s, 3H); 5.4 (dd, J=6, 3, 12.6Hz, 1H); 7-7.1(m, 6H); 7.6(d, J=8.7Hz, 2H)
45 38	84-90	3308, 3224, 1700, 1317, 1147, 1094	(d ₄ -CH ₃ OH): 3.1(dd, J=6, 18.3Hz, 1H); 3.9 (s+dd, 4H); 5.7(dd, J=6, 12.9Hz, 1H); 7.2-7.4 (m, 7H); 7.75(d, J=8.7Hz, 2H)
50 39	155-160	1741, 1561, 1260, 1226, 1135, 1089	2.3(s, 3H); 3(s, 3H); 3.1(dd, J=6, 18.3Hz, 1H); 3.75(dd, J=12.6, 18.3Hz, 1H); 5.4(dd, J=6, 12.6Hz, 1H); 7-7.25(m, 6H); 7.7(d, J=8.7Hz, 2H)
55 40	200-5	3431, 3285, 1647, 1592, 1328, 1142	(d ₄ -CH ₃ OH): 3.1(dd, J=6, 18.3Hz, 1H); 3.9 (dd, J=12.9, 18.3Hz, 1H); 5.7(dd, J=6, 12.9Hz, 1H); 7.2-7.5(m, 7H); 7.75(d, J=8.7Hz, 2H)
41	210-5	3450, 3337, 1656, 1596, 1345, 1141	(d ₄ -CH ₃ OH): 2.4(s, 3H); 3.05(dd, J=6, 17.7Hz, 1 H); 3.8(dd, J=12.9, 17.7Hz, 1H); 5.6(dd, J=6, 12.9 Hz, 1H); 7.2-7.3 (m, 6H) 7.75(d, J=8.7Hz, 2H)

Table 2 (continued)

Examp le	m. p. °C	IR (KBr) cm ⁻¹	¹ H-RMN (CDCl ₃) δ ppm
42	128-132	3440, 3200, 1680, 1590, 1135	2.3(s,3H); 3(s,3H); 3.1(dd,J=6.3,18.6Hz,1H); 3.8(dd,J=12.6, 18.6Hz,1H); 5.4(dd,J=6.3, 12.6Hz,1H); 5.6(s ancho,1H); 6.7(s ancho,1H); 7-7.2(m, 6H); 7.7(d,J=8.7Hz, 2H)
43	162-4	2220, 1593, 1500, 1389, 1296, 1143	2.3(s,3H); 3-3.1(s+dd,4H); 3.75(dd,J=12.6, 18Hz,1H); 5.5(dd,J=6.3, 12.6Hz,1H); 7-7.2(m, 6H); 7.7(d,J=8.7Hz,2H)
44	152-5	3318, 3240, 1594, 1323, 1178, 1121, 1065, 549	2.2(s,6H); 3(dd,J=6.3, 18.3Hz,1H); 3.7(dd,J=12.6, 18.3Hz,1H); 4.7(s ancho,2H); 5.4(dd,J=6.3, 12.6Hz,1H); 6.95(s+d,J=7.8Hz, 2H); 7.1(2d,J=7.8, 8.7Hz,3H); 7.7(d,J=8.7Hz,2H)
45	170-5	3360, 3267, 1595, 1507, 1329, 1255, 1159, 619	2.2(s,3H); 3(dd,J=7.2, 18Hz,1H); 3.6-3.8(s+dd,4H); 4.6(b s, 2H); 5.35(dd,J=7.2, 12.9Hz,1H); 6.75(d,J=7.8Hz,1H); 7(s+d, 2H); 7.1(d,J=8.7Hz,2H); 7.7(d,J=8.7Hz,2H)
46	108-14	3383, 2270, 1595, 1519, 1329, 1277, 1160, 1066	3(dd,J=6.6 18.3Hz,1H); 3.75(dd,J=12.3, 18.3 Hz,1H); 3.9(s,3H); 5.4(dd,J=6.6, 12.3Hz,1H); 6.95(m,3H); 7.05(d,J=8.7Hz, 2H); 7.7(d,J=8.7Hz,2H)
47	157-9	3357, 3267, 1630 1595, 1508, 1330, 1264, 1158, 1066	3.05(dd,J=6.3, 18Hz,1H); 3.7-3.8(s+dd, 4H); 4.8(s ancho,2H); 5.7(dd,J=6.3, 12.9Hz, 1H); 6.6-6.7(m,2H); 6.95(t,J=8.7Hz,1H); 7.05(d,J=9Hz,2H); 7.7(d,J=9Hz,2H)
48	121-6	3376, 3268, 1593, 1507, 1329, 1160	2.9(dd,J=6, 18Hz,1H); 3.65(dd,J=12.6, 18Hz,1H); 3.75(s,3H); 3.85(s,3H); 4.9(s, 2H); 5.65(dd,J=6, 12.6Hz,1H); 6.35(d,J=8.7Hz,1H); 6.5(s,1H); 6.9(d,J=8.7Hz,1H); 7(d,J=8.7Hz,2H); 7.7(d,J=8.7Hz,2H)
49	179-82	3317, 3231, 1593, 1507, 1326, 1178	(d ₆ -DMSO): 2.95(dd,J=5.4, 18Hz,1H); 3.7-3.8(m,4H); 5.8(dd,J=5.4, 12.6Hz,1H); 6.7(dd,J=8.1, 10.5Hz,1H); 6.9-7.1(m,6H); 7.6(d,J=8.7Hz,2H)
50	181-3	3348, 3268, 1593, 1321, 1165	2.25(s,3H); 2.35(s,3H); 2.85(dd,J=6.9, 18Hz,1H); 3.7(dd,J=12.6, 18Hz,1H); 5.45(dd,J=6.9, 12.6Hz,1H); 6.5(t,J=54Hz,1H); 6.8-6.9(m,4H); 7(s,1H); 7.85(d,J=9Hz,2H)
51	159-61	3382, 3285, 1595, 1514, 1328, 1161	3(dd,J=6.3, 17.7Hz,1H); 3.8(dd,J=12.6, 17.7Hz,1H); 4.7(s,2H); 5.7(dd,J=6.3, 12.6Hz,1H); 6.8(m,1H); 6.9(m, 1H); 7 (d,J=9Hz,2H); 7.75(d,J=9Hz,2H)
52	167-9	3318, 3239, 1593, 1503, 1492, 1321, 1068	(d ₆ -DMSO): 3(dd,J=6.3, 18.3Hz,1H); 3.95(dd,12.9, 18.3Hz,1H); 5.95(dd,J=6.3, 12.9Hz,1H); 7(d,J=8.7Hz,2H); 7.1-7.2(m, 4H); 7.55(d,J=8.4Hz,1H); 7.65(d,J=8.7Hz, 2H)

Table 2 (continued)

Examp le	m. p. °C	IR (KBr) cm ⁻¹	¹ H-RMN (CDCl ₃) δ ppm
53	170-3	3425, 3284, 1595, 1330, 1138	(d ₆ -DMSO): 3.2(dd, J=5.7, 18Hz, 1H); 3.9 (dd, J=12.9, 18Hz, 1H); 6(dd, J=5.7, 12.9Hz, 1H); 7.1(m, 4H); 7.4-7.7(m, 4H); 7.8(d, J=10.8Hz, 1H)
54	212-4	3376, 3277, 1597, 1332, 1274, 1132	2.8(dd, J=6.3, 18.5Hz, 1H); 3.7(dd, J=13, 18.5Hz, 1H); 5.75(dd, J=6.3, 13Hz, 1H); 6.1 (s, 2H); 6.8(d, J=8.5Hz, 2H); 7.2(d, J=8.3Hz, 1H); 7.6(d, J=8.5Hz, 2H); 7.65(d, J=8.3Hz, 1H); 7.9(s, 1H)
55	193-5	3353, 3270, 1593, 1509, 1321, 1141	(d ₆ -DMSO): 2.3(s, 3H); 2.9(dd, J=6.1, 12.2Hz, 1H); 3.95(dd, J=12.2, 12.9Hz, 1H); 5.95(dd, J=6.1, 12.9Hz, 1H); 6.65(s ancho, 1H); 7(d, J=8.8Hz, 2H); 7.1-7.2(m, 4H); 7.65 (d, J=8.8Hz, 2H)
56	148-50	3384, 3266, 1593, 1324, 1252, 1166	2.35(s, 3H); 2.9(dd, J=5.6, 18Hz, 1H); 3.7-3.8 (m, 4H); 4.9(banda ancha, 2H); 5.5(dd, J=5.6, 12.6Hz, 1H); 6.6(dd, J=2.2, 8.5Hz, 1H); 6.8(s, 1H); 6.85-6.95(2d, 3H); 7.7(d, J=9Hz, 2H)
57	157-60	3384, 3346, 3277, 3255, 1596, 1503, 1341, 1158	3(dd, J=6.1, 17.8Hz, 1H); 3.7(dd, J=12.4, 17.8Hz, 1H); 4.75(s, 2H); 5.6(dd, J=6.1, 12.4Hz, 1H); 6.5(t, J=54Hz, 1H); 6.8-7(m, 5H); 7.7(d, J=8.8Hz, 2H)
58	174-7	3384, 3261, 1596, 1329, 1117	2.95(dd, J=5.6, 17.3Hz, 1H); 3.75(dd, J=12.4, 17.3Hz, 1H); 4.7(s ancho, 2H); 5.8 (dd, J=5.6, 12.4Hz, 1H); 6.95(d, J=8.3Hz, 2H); 7.2(m, 2H); 7.5(d, J=7.5Hz, 1H); 7.75(d, J=8.3Hz, 2H)
59	105-6	1596, 1510, 1314, 1264, 1150, 845	3(s+dd, 4H); 3.6 (dd, J=12.2, 17.6Hz, 1H); 5.6 (dd, J=6.2, 12.2Hz, 1H); 6.65 (t, J=9Hz, 1H); 6.75 (t, J=8Hz, 1H); 7.35 (m, 3H); 7.8 (d, J=8.3Hz, 2H)
60	157-9	3354, 3268, 1594, 1325, 1122, 753	2.95(dd, J=6.6, 18.5Hz, 1H); 3.85(dd, J=12.7, 18.5Hz, 1H); 4.8(s, 2H); 5.8 (dd, J=6.6, 12.7Hz, 1H); 6.9-7(m, 3H); 7.1-7.3(m, 2H); 7.45(d, J=7.8Hz, 1H); 7.7(d, J=8.6Hz, 2H)
61	180-5	3407, 3295, 1593, 1334, 1161	(d ₄ -CH ₃ OH): 3.2 (dd, J=6.3, 18.1Hz, 1H); 3.95(dd, J=12.9, 18.1Hz, 1H); 6(dd, J=6.3, 12.9Hz, 1H); 7.2(d, J=8.8Hz, 2H); 7.3(m, 2H); 7.4(d, J=10.3Hz, 1H); 7.8(d, J=8.8Hz, 2H)
62	154-60	3406, 3262, 1593, 1330, 1155	2.4(s, 3H); 2.9(dd, J=6.6, 17.8Hz, 1H); 3.75 (dd, J=12.7, 17.8Hz, 1H); 4.8(s, 2H); 5.5(dd, J=6.6, 12.7Hz, 1H); 6.8-7(m, 5H); 7.7(d, J=8.8Hz, 2H)
63	166-7	3430, 3298, 1593, 1508, 1334, 1161, 1123	2.3(s, 3H); 3(dd, J=6.3, 18.3Hz, 1H); 3.75(dd, J=12.7, 18.3Hz, 1H); 4.65(s, 2H); 5.7(dd, J=6.3, 12.7Hz, 1H); 6.85-7(m, 3H); 7.05(d, J=8.8Hz, 2H); 7.7(d, J=8.8Hz, 2H)

Table 2 (continued)

Examp le	m. p. °C	IR (KBr) cm ⁻¹	¹ H-RMN (CDCl ₃) δ ppm
5 64	172-4	3302, 1722, 1593, 1506, 1337, 1165	2 (s, 3H) ; 3(dd,J=6.6, 18Hz,1H); 3.8(dd, J=12.9, 18Hz,1H); 5.7(dd,J=6.6, 12.9Hz, 1H); 6.8-6.95(m,2H); 7-7.1 (m,3H); 7.85(d, J=8.7Hz,2H); 8.1(s,1H)
10 65	117-21	1594, 1492, 1310, 1257, 1154, 1063	2.95(dd,J=7.3, 17.8Hz,1H); 3(s,3H); 3.7(dd, J= 12.7, 17.8Hz,1H); 5.45(dd,J=7.3, 12.7Hz,1H); 6.8(d,J=8.8Hz,2H); 7.1(d, J=8.8Hz,2H); 7.4(d,J=8.3Hz,2H); 7.9(d, J=8.3Hz,2H)
15 66	114-5	1598, 1503, 1275, 1156, 1079, 749	2.95(dd,J=7.6, 17.8Hz,1H); 3(s,3H); 3.7 (dd, J= 12.7, 17.8Hz,1H); 5.45(dd,J=7.6, 12.7Hz,1H); 6.9(m,3H); 7.15(t,J=7.8Hz,2H); 7.4(d,J=8,1Hz,2H); 7.9(d,J=8.1Hz,2H)
20 67	98-9	1606, 1503, 1317, 1148, 1123, 762	3(s+dd,4H); 3.65(dd,J= 13.1, 17.1Hz,1H); 5.8(dd,J=7.6, 13,1Hz,1H); 6.9(m,2H); 7(t, J=8.1Hz,1H); 7.3(d,J=8.1Hz,2H); 7.45(t, J=8.3Hz,1H); 7.8(d,J=8.1Hz,2H)
25 68	104-8	1617, 1496, 1310, 1253, 1154, 1113, 809	2,3(s,3H); 3(m,4H); 3.5(dd,J= 11.7, 17.1Hz, 1H); 5.45(t,J=11.7Hz,1H); 6.75(d,J=8.5Hz, 1H); 7(d,J=8.5Hz,1H); 7.1(s,1H); 7.45(d, J=8Hz,2H); 7.9(d,J=8Hz,2H)
30 69	116-7	1616, 1587, 1498, 1310, 1155, 828	2.9(dd,J=7.5, 16.8Hz,1H); 3(s,3H); 3.7(dd, J= 12.7, 16.8Hz,1H); 5.4(dd,J=7.5, 12.7Hz, 1H); 6.6(m,2H); 6.7(d,J=11Hz,1H); 7.1(dd, J=7.6, 14.9Hz,1H); 7.4(d,J=8Hz,2H); 7.9(d, J=8Hz,2H)
35 70	114-6	1597, 1315, 1149, 1072, 959, 789	2.25(s,3H); 2.9(dd,J=7.6, 17.8Hz,1H); 3(s, 3H); 3.7(dd,J= 12.9, 17.8Hz,1H); 5.45(dd, J=7.6, 12.9Hz,1H); 6.6(d,J=7.8Hz,1H); 6.7 (d,J=7.8 Hz,1H); 6.9(s,1H); 7(t,J=7.8Hz, 1H); 7.45(d,J=8Hz,2H); 7.9(d,J=8Hz,2H)
40 71	132-3	1601, 1509, 1314, 1154, 1113, 809	2.2(s,3H); 2.3(s,3H); 3(m,4H); 3.5(dd,J= 11.7, 16.6Hz, 1H); 5.4(t,J=11.7Hz,1H); 6.8 (m,2H); 6.9(s,1H); 7.5(d,J=8Hz,2H); 7.85(d, J=8Hz,2H)
45 72		1617, 1589, 1483, 1313, 1149, 759 (film)	2.95(s,3H); 3.15(dd,J=6.5, 17.8Hz,1H); 3.65(dd,J= 12.7, 17.8Hz,1H); 5.95(dd, J=6.5, 12.7Hz,1H); 6.95(d,J=7.8Hz,1H); 7.1 (t,J=7.3Hz,1H); 7.2(m,2H); 7.35(d,J=8.3Hz, 2H); 7.8(d,J=8.3Hz,2H)
50 73		1598, 1496, 1406, 1312, 1151, 757 (film)	2.3(s,3H); 3(s+dd,4H); 3.5(dd,J= 11.7, 17.8Hz,1H); 5.5(t,J=11.7Hz,1H); 6.85 (d, J=7.8Hz,1H); 7(m,2H); 7.1(d,J=6.1Hz,1H); 7.5(d,J=8.3Hz,2H); 7.85(d,J=8.3Hz,2H)
55 74	103-6	1625, 1483, 1312, 1150, 1130, 819	3(s,3H); 3.15(dd,J=5.9, 17.8Hz, 1H); 3.7(dd, J= 11.7, 17.8Hz, 1H); 5.95 (dd, J=5.9, 11.7Hz,1H); 7.05 (d,J=8.8Hz,1H); 7.2(m, 2H); 7.3(d,J=8.1Hz,2H); 7.8(d,J=8.1Hz,2H)

Table 2 (continued)

Examp le	m. p. °C	IR (KBr) cm ⁻¹	¹ H-RMN (CDCl ₃) δ ppm
5 75		1603, 1318, 1148, 1060, 955, 760 (film)	3(s,3H); 3.1(dd,J=8.8, 16.4Hz,1H); 3.6(dd, J= 12.7, 16.4Hz,1H); 5.6(dd,J=8.8, 12.7Hz, 1H); 7(d,J=7.8Hz,1H); 7.15(t,J=8.1Hz,1H); 7.3(t,J=8.1Hz,1H); 7.4(d,J=8.3Hz,2H); 7.6 (d,J=7.8Hz,1H); 7.8(d,J=8.3Hz,2H)
10 76	138-40	3340, 3249, 1508, 1332, 1165, 1121, 832	(d ₆ -DMSO): 3(dd, J=7.6, 16.1Hz,1H); 3.8 (dd, J=12.9, 16.1Hz,1H); 5.8(dd, J=7.6,12.9Hz,1H); 6.9(m,2H); 7.1(t, J=8.9Hz,2H); 7.35(s ancho, 2H); 7.4(d, J=8.3Hz,2H); 7.8(d,J=8.3Hz,2H)
15 77	132-5	1598, 1508, 1303, 1149, 744	2.1(s,3H); 2.7(dd,J=7.8, 17.3Hz, 1H); 3(s, 3H); 3.5(dd,J=12.2, 17.3Hz,1H); 5.1(dd, J=7.8, 12.2Hz,1H); 6.8 (t, J=7.1Hz,1H); 6.9 (d, J=8Hz, 2H); 7.1(t, J=8Hz,2H); 7.5(d, J=8Hz,2H); 7.9(d, J=8Hz,2H)
20 78	155-60	1510, 1290, 1140, 800, 540	2.8(dd,J=8.3, 17.8Hz,1H); 3(s,3H); 3.5(dd, J=12.2, 17.8Hz, 1H); 5(dd,J=8.3, 12.2Hz, 1H); 6.8-6.95(m,5H); 7.5 (d, J=8.3Hz,2H); 7.9(d,J=8.3Hz,2H)
25 79	173-4	3330, 3250, 1617, 1593, 1506, 1329, 1121, 1099, 855	3(dd,J=6.3, 11.4Hz,1H); 3.8(dd,J=11.4, 12.6Hz, 1H); 4.8(s ancho,2H); 5.7(dd,J=6.3, 12.6Hz,1H); 6.8-6.95(m,2H); 7-7.1(m,3H); 7.7(d,J=8.7Hz,2H)
30 80	173-4	3330, 3250, 1617, 1593, 1506, 1329, 1121, 1099, 855	3(dd,J=6.3, 11.4Hz,1H); 3.8(dd,J=11.4, 12.6Hz, 1H); 4.8(s ancho,2H); 5.7(dd,J=6.3, 12.6Hz,1H); 6.8-6.95(m,2H); 7-7.1(m,3H); 7.7(d,J=8.7Hz,2H)
35 81	113-5	1508, 1315, 1155, 1133, 1067, 831	2.9(dd,J=8.4, 17.4Hz,1H); 3(s,3H); 3.7(dd, J= 12.6, 17.4Hz,1H); 5.4(dd,J=8.4, 12.6Hz, 1H); 6.9(m,4H); 7.45(d,J=8.4Hz,2H); 7.95 (d,J=8.4 Hz,2H)
40 82	113-4	1508, 1315, 1155, 1133, 1067, 827	2.9(dd,J=8.4, 17.4Hz,1H); 3(s,3H); 3.7(dd, J= 12.6, 17.4Hz,1H); 5.4(dd,J=8.4, 12.6Hz, 1H); 6.9(m,4H); 7.45(d,J=8.4Hz,2H); 7.95 (d,J=8.4 Hz,2H)
45 83	86-9	1596, 1510, 1314, 1264, 1150, 845	3(s+dd, 4H); 3.6 (dd, J=12.2, 17.6Hz, 1H); 5.6 (dd, J=6.2, 12.2Hz, 1H); 6.65 (t, J=9Hz, 1H); 6.75 (t, J=8Hz, 1H); 7.35 (m, 3H); 7.8 (d, J=8.3Hz, 2H)
50 84	84-6	1596, 1510, 1314, 1264, 1150, 845	3(s+dd, 4H); 3.6 (dd, J=12.2, 17.6Hz, 1H); 5.6 (dd, J=6.2, 12.2Hz, 1H); 6.65 (t, J=9Hz, 1H); 6.75 (t, J=8Hz, 1H); 7.35 (m, 3H); 7.8 (d, J=8.3Hz, 2H)

[0020] In human therapy, the administration dose of the compounds of the present invention depends on the seriousness of the condition to be treated. It will normally lie between 10 and 500 mg/day. The compounds of the invention can be administered as a single active principle or together with another product, in order to obtain a synergy. The compounds of the invention, with a suitable pharmacological formulation, may be given orally, transdermally, parenterally, subcutaneously, intranasally, intramuscularly or intravenously. Pharmaceutical compositions containing the compounds of general formula (I) are described in our patent application WO 99/62884.

Biological evaluation

[0021] The compounds with the general formula (I) are useful for treatment of preneoplastic or neoplastic processes, angiogenesis, cachexia and processes related to tumour necrosis factor (TNF) and, in general, processes that can benefit from inhibition of the expression of the gene in charge of the synthesis of cyclooxygenase-2 (COX-2). In order to demonstrate these activities below are provided, by way of example, several pharmacological tests.

Inhibition of the induction of COX-2

[0022] In order to determine the inhibition capability of the transcriptional induction of cyclooxygenase-2 a cell system was used of stable transfectant JURKAT cells with the promoter of the gene COX-2 associated to the gene for luciferase. Three independent clones were used (C3, C7 and F9) which differ in their basal luciferase activity ranging from 4500 to 180.000 RLU/10⁵ cells, which are increased as a response to stimulant agents such as proinflammatory type activators of the cell signalling paths as forbol esters (TPA) and ionofors (ionomycin).

[0023] For the test the cells were pre-treated for 1 hour with the compounds to test and then stimulated with TPA + ionomycin for 6 hours. Cell extracts were then obtained in which the luciferase activity was examined and the protein concentration determined. Inhibition of the luciferase activity gives an indication of the inhibition of the induction of COX-2.

[0024] As an example of the activity of the compounds with general formula (I), we shown below the results obtained with the compound of Example 10, which show a clear inhibition of the induction of COX-2.

Example 10 (Concentration µg/ml)	Inhibition of the activity of luciferase (%)		
	Clone C7	Clone C9	Clone F9
0.5	20%	40%	32%
5	55%	75%	65%
50	85%	85%	95%
IC-50 (µg/ml)	5.8	0.9	1.8

Anti-tumoral activity in the human colon carcinoma

[0025] The anti-tumoral activity of the compounds with general formula (I) was studied, determining their effect on cell lines of human colon carcinoma (TD 20 and NC 59). The two cell lines have the wild protein K-Ras. TD20 contains a mutation of the p53 suppressor gene, while NC59 has the p53 wild protein.

[0026] Both cell lines were cultured in a DMEM medium (Life Technologies) supplemented with 10% foetal bovine serum (Life Technologies) at 37°C and 5% CO₂.

[0027] Cytotoxicity tests were carried out using the XTT kit (Boehringer-Manheim) which measures the cell capability to metabolise a tetrazoyl salt to formazan.

Concentration (µM)		% Viability of colorectal cancer cells ± SD	
		NC59	TD 20
Example 3	1	99.64 ± 0.51	98.58 ± 2.83
	20	76.52 ± 8.70	84.46 ± 3.05
	30	56.50 ± 0.25	66.34 ± 5.84
	40	16.74 ± 10.53	27.38 ± 4.12
	60	1.16 ± 0.83	1.79 ± 2.09
	100	0 ± 0	0.69 ± 0.01
		IC-50 = 29.87	IC-50 = 33.87
Example 10	1	92.09 ± 9.35	95.03 ± 8.87
	20	76.14 ± 7.17	90.24 ± 5.97
	40	15.77 ± 9.37	43.13 ± 13.77
	60	2.59 ± 1.54	5.42 ± 4.11
	80	1.66 ± 1.57	3.22 ± 3.46

(continued)

Concentration (μM)		% Viability of colorectal cancer cells \pm SD	
		NC59	TD 20
		IC-50 = 27.18 μM	IC-50 = 37.92 μM

[0028] As an example of the activity of the compounds with general formula (I), the compounds of examples 3 and 10 showed cytotoxic activity on both human colon carcinoma cell lines. Their IC₅₀ on cell line NC59 was 30 μM and 27 μM and on line TD20 it was 34 μM and 38 μM , respectively.

[0029] In order to obtain a deeper knowledge of the action mechanism of these compounds the capability to induce apoptosis in the tumour cell line TD20 of the compound of example 3 was studied (dose 100 μM). In these conditions 20% apoptotic cells were found after 24h and 80% after 48h, while in the cells treated with a carrier the apoptotic cells did not exceed 1%. Cytotoxicity levels, measured by XTT, were similar to apoptosis levels, suggesting that the cytotoxicity activity of example 3 is due to their ability to induce apoptosis.

[0030] The signal transduction paths associated to the apoptosis process were then studied. After exposing NC59 cells to a 100 μM concentration of the compound of example 3, the expression levels were studied for p53, FAK and β -actine and the activation level of MAP kinases, JNK and PKB/Akt, after 5 and 20 hours of exposure. The results demonstrated the activation of signal transduction paths other than p53, JNK or p38, which are the paths activated by conventional genotoxic drugs (e.g. 5-FU).

[0031] In summary; it can be said that the compounds of examples 3 and 10 are effective anti-tumoral agents for human colon carcinoma, which suggests the possibility of using the compounds with general formula (I) not only as chemopreventives but in established colon cancer. In addition, their anti-tumoral effect is mediated by apoptosis and the activation of the transduction paths is effected by signals other than p53, JNK or p38, which suggests that these compounds may constitute an addition to current chemotherapy protocols as they have a different cytotoxic action mechanism.

Anti-tumoral activity in mammary carcinoma

[0032] The anti-tumoral activity of the compounds with general formula (I) was studied, determining their effect on a mammary carcinoma cell line (MDAMB 453). The cell line was cultured in a DMEM medium (Life Technologies) supplemented with 10% foetal bovine serum (Life Technologies) at 37°C and 5% CO₂.

[0033] Cytotoxicity tests were carried out using the XTT kit (Boehringer-Manheim) which measures the cell capability to metabolise a tetrazolyl salt to formazan.

Concentration (μM)		% Viability of mammary cancer cells \pm SD	
		MDAMB 453	
Example 3	1	94.76 \pm 8.71	
	20	31.52 \pm 9.12	
	40	12.77 \pm 4.80	
	60	5.97 \pm 5.06	
	80	2.84 \pm 1.71	
		IC-50 = 12.87 μM	
Example 10	1	97.53 \pm 3.25	
	20	42.75 \pm 9.31	
	40	33.30 \pm 7.34	
	60	8.25 \pm 6.82	
	80	5.8 \pm 4.76	
		IC-50 = 17.88 μM	

[0034] As an example of the activity of the compounds with general formula (I), the compounds of Examples 3 and 10 showed cytotoxic activity on the mammary carcinoma cell line, with an IC₅₀ of 3 μM (Example 3) and 18 μM (Example

10).

[0035] In summary, it can be said that the compounds of examples 3 and 10 are effective anti-tumoral agents for mammary carcinoma, which suggests the possibility of using the compounds with general formula (I) not only as chemopreventives but in established mammary carcinoma.

Antiangiogenic activity

[0036] This activity has been studied determining the inhibition of the induction of the expression of VEGF. The increased expression of vascular-endothelial growth factor (VEGF) has been related to tumour progression and angiogenesis. VEGF is a proangiogenic factor, promoting mitogenesis, migration and an increased vascular permeability of in vitro endothelial cells. It has been shown recently that COX-2 can regulate the angiogenesis process induced by colon cancer cells, increasing the expression of proangiogenic factors by said cells. Inhibition of COX-2 may block this process, inhibiting the expression of some of these factors, such as VEGF.

[0037] In turn, VEGF also induces the expression of Tissue Factor (TF) in monocyte membranes, epithelial cells and endothelium. Although the main function of TF is to initiate the coagulation cascade, it can transduce intracellular signals participating in metastasis and angiogenesis associated to tumours. TF facilitates in vivo growth of the tumour, favouring angiogenesis. It has been demonstrated that tumour cells transfected with TF produce greater vascularization.

[0038] In order to study the antiangiogenic activity of the products with general formula (I), the expression of the VEGF promoter was studied in a basal and stimulated situation using the Caco-2 human colon carcinoma cell line, temporally transfected with a vector containing the promoter of the human VEGF gene. Once the test conditions were established the capability of the product studied to inhibit the expression of the VEGF and TF genes was studied by measuring the luciferase activity of their promoters.

[0039] In the test 1.25×10^5 Caco-2 cells were used temporally transfected with the corresponding DNA in 500 μ l of DEMEM-10% FCS medium in 24 dimple plates. The cells were pre-treated for 1 hour with the compounds to be tested, and later stimulated with TPA for 16 hours. Afterwards cell extracts were obtained and their luciferase activity examined, determining the protein concentration.

[0040] By way of example of the activity of the compounds with general formula (I), below are provided the results obtained for the compounds of examples 3 and 10, which show a clear antiangiogenic effect as both VEGF and TF are inhibited.

Compound	Inhibition of the induction of	
	VEGF	TF
	IC-50 (μ g/ml)	IC-50 (μ g/ml)
Example 3	20	25
Example 10	25	22

Inhibition of tumour necrosis factor - α (TNF- α)

[0041] Tumour necrosis factor - α (TNF- α) is a cytokine, a powerful proinflammatory and immunomodulator involved in various inflammatory conditions such as rheumatoid arthritis, CROHN's disease, multiple sclerosis and cachexia associated with cancer, as well as in human immunodeficiency associated to viral infections. TNF- α was originally described due to its capacity to induce haemorrhagic necrosis of certain tumours in animals treated with lipopolysaccharide (LPS). It was also called cachectin, as it is a circulating mediator of the wear syndrome related to certain parasitary diseases. Cachexia, or the wear resulting from TNF, is related to its property of increasing the lipase of lipoprotein and for this reason exhausts adipose cells. TNF- α is produced predominantly by macrophages when activated by a great variety of stimuli, such as the presence of bacterial or mycobacterial proteins, fungal antigens, virus, C5a complement or gamma interferon.

[0042] TNF- α is one of the mediators of Gram- bacterial endotoxic shock, and seems to be responsible for fever, metabolic acidosis, diarrhoea, hypertension, disseminated vascular coagulation and in certain cases even death. In addition, TNF- α can lead to the activation of neutrophils, inducing the geneic expression of IL-1, increase the expression of MHC antigens (with Class I major histocompatibility) in endothelial cells and is involved in reabsorption of the bone marrow and in production of PGE₂ and collagenase of synovial cells and human fibroblasts. Thus, products capable of antagonising the activity of this mediator can have clinical value to combat their lethal effects (C.A. Mc Intyre et al: *Drugs News and Perspectives* 1992 5 (4): 207-213; A.J.H. Gearing et al: *Nature* 1994 370: 555-557; M.A. Pahlavani: *Drugs of Today* 1993 29 (8): 525-533).

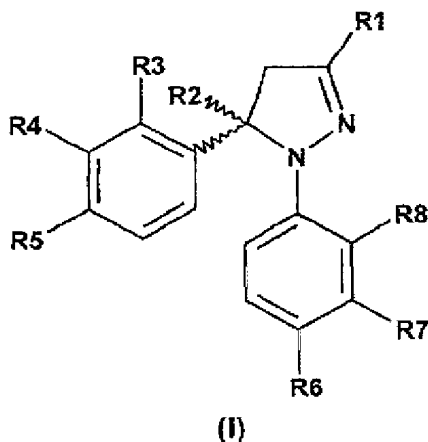
[0043] The study of the inhibitory activity of TNF- α has been performed according to the method described by P. Klemen et al. (*Europ. J. Pharmacol.* 1995 **281**: 69-74), consisting of determining the production of TNF- α in the localised area where the inflammation is acute, specifically using the zymosan inflated air pouch model in mice. The TNF- α present in the inflammatory exudates produced in said pouch as a result of the stimulation with zymosan was determined. The analytical determination of TNF- α was performed by ELISA.

by way of example of the activity of the compounds with general formula (I), below are shown the results obtained with the compound of Example 10, which shows a considerable TNF- α inhibitory activity, very well correlated with the dose.

Example 10 Doses (mg/kg, i.p.)	Air pouch model in mice % Inhibition of TNF- α in inflammatory exudate stimulated by zymosan
0.039	12.6 \pm 2.6
0.156	15.7 \pm 4.9
0.625	46.8 \pm 12.5
2.5	58.8 \pm 13.6
DE-50 = 1.20 mg/kg, i.p. (r = 0.957) (*)	
i.p.: intraperitoneal	

Claims

1. Use of a derivative of pyrazoline with the general formula (I)



wherein

R₁ represents an atom of hydrogen, a methyl, fluoromethyl, difluoromethyl, trifluoromethyl group, carboxylic acid, lower alkyl carboxylate with 1 to 4 carbon atoms, carboxamide or cyano group,

R₂ represents an atom of hydrogen or a methyl group,

R₃, R₄, R₇ and R₈, like or different, represent an atom of hydrogen, chlorine, fluorine, a methyl, trifluoromethyl or methoxy group,

R₅ represents an atom of hydrogen, chlorine, fluorine, a methyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylaminosulphonyl group,

R₆ represents an atom of hydrogen, chlorine, fluorine, a methyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylaminosulphonyl group,

with the condition that one of the substituents R₅ or R₆ is a methylsulphonyl, aminosulphonyl or acetylaminosulphonyl group, and

with the condition that when R₁ represents a methyl group

R₂ represents an atom of hydrogen or a methyl group,

R₃ and R₈, like or different, represent an atom of hydrogen, chlorine, fluorine, a methyl or trifluoromethyl group,

R₄ represents an atom of hydrogen, fluorine, a methyl, trifluoro-methyl or methoxy group,

R₅ represents a fluorine atom, a trifluoromethyl, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylamino sulphonyl group,

R₆ represents an atom of hydrogen, chlorine, fluorine, a methyl, trifluoromethyl, methoxy, trifluoromethoxy, methylsulphonyl, aminosulphonyl or acetylamino sulphonyl group,

with the condition that one of the substituents R₅ or R₆ is a methylsulphonyl, aminosulphonyl or acetylamino sulphonyl group, and

R₇ represents an atom of hydrogen, chlorine, fluorine, a methyl, trifluoromethyl or methoxy group;

Or one of their physiologically acceptable salts,

in the preparation of a medicament for preventing or treating cell proliferation diseases, particularly for preventing or treating preneoplastic or neoplastic processes, tumoral angiogenesis, cachexia and processes related to tumour necrosis factor (TNF) and, in general, processes that can benefit from inhibition of the expression of the gene responsible for synthesising cyclooxygenase-2 (COX-2) in mammals, including man.

2. Use according to claim 1 of a compound with the general formula (I) selected from among the group comprised of:

- [1] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(4-methylphenyl)-3-trifluoromethyl-1H-pyrazol
- [2] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-methyl-5-(4-methylphenyl)-3-trifluoromethyl-1H-pyrazol
- [3] 1-(4-Aminosulphonylphenyl)-5-(2,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol
- [4] 4,5-Dihydro-1-(4-methylphenyl)-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
- [5] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-phenyl-3-trifluoromethyl-1H-pyrazol
- [6] 4,5-Dihydro-5-phenyl-1-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
- [7] 4,5-Dihydro-5-(4-methylphenyl)-1-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
- [8] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(4-fluorophenyl)-3-trifluoromethyl-1H-pyrazol
- [9] 4,5-Dihydro-5-(4-fluorophenyl)-1-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
- [10] 4,5-Dihydro-1-(4-fluorophenyl)-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
- [11] 1-(4-Aminosulphonylphenyl)-5-(3,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol
- [12] 5-(2,4-Dichlorophenyl)-4,5-dihydro-1-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
- [13] 1-(4-Aminosulphonylphenyl)-5-(2,4-dichlorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol
- [14] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(2-methylphenyl)-3-trifluoromethyl-1H-pyrazol
- [15] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(3-methylphenyl)-3-trifluoromethyl-1H-pyrazol
- [16] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(2-fluorophenyl)-3-trifluoromethyl-1H-pyrazol
- [17] 4,5-Dihydro-5-(2-fluorophenyl)-1-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
- [18] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(3-fluorophenyl)-3-trifluoromethyl-1H-pyrazol
- [19] 4,5-Dihydro-5-(3-fluorophenyl)-1-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
- [20] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazol
- [21] 1-(4-Aminosulphonylphenyl)-5-(3-chloro-4-fluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol
- [22] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-3-trifluoromethyl-5-(4-trifluoromethoxyphenyl)-1H-pyrazol
- [23] 1-(4-Aminosulphonylphenyl)-5-(2,3-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol
- [24] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(2,4-dimethylphenyl)-3-trifluoromethyl-1H-pyrazol
- [25] 5-(3,4-Difluorophenyl)-4,5-dihydro-1-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
- [26] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(4-fluorophenyl)-3-methyl-1H-pyrazol
- [27] 4,5-Dihydro-5-(4-fluorophenyl)-3-methyl-1-(4-methylsulphonylphenyl)-1H-pyrazol
- [28] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-3-methyl-5-(4-methylphenyl)-1H-pyrazol
- [29] 4,5-Dihydro-3-methyl-5-(4-methylphenyl)-1-(4-methylsulphonylphenyl)-1H-pyrazol
- [30] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-3-methyl-5-(4-trifluoromethylphenyl)-1H-pyrazol
- [31] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-phenyl-1H-pyrazol
- [32] 4,5-Dihydro-5-phenyl-1-(4-methylsulphonylphenyl)-1H-pyrazol
- [33] 4,5-Dihydro-3-methyl-1-(4-methylsulphonylphenyl)-5-(4-trifluoromethylphenyl)-1H-pyrazol
- [34] 1-(4-aminosulphonylphenyl)-4,5-dihydro-5-(4-methylphenyl)-1H-pyrazol-3-carboxylic acid
- [35] 1-(4-aminosulphonylphenyl)-4,5-dihydro-5-phenyl-1H-pyrazol-3-carboxylic acid
- [36] 4,5-dihydro-5-(4-methylphenyl)-1-(4-methylsulphonylphenyl)-1H-pyrazol-3-carboxylic acid
- [37] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(4-methylphenyl)-1H-pyrazol-3-methyl carboxylate
- [38] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-phenyl-1H-pyrazol-3-methyl carboxylate
- [39] 4,5-Dihydro-5-(4-methylphenyl)-1-(4-methylsulphonylphenyl)-1H-pyrazol-3-methyl carboxylate
- [40] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-phenyl-1H-pyrazol-3-carboxamide
- [41] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(4-methylphenyl)-1H-pyrazol-3-carboxamide
- [42] 4,5-Dihydro-5-(4-methylphenyl)-1-(4-methylsulphonylphenyl)-1H-pyrazol-3-carboxamide
- [43] 3-Cyano-4,5-dihydro-5-(4-methylphenyl)-1-(4-methylsulphonylphenyl)-1H-pyrazol

- [44] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(3,4-dimethylphenyl)-3-trifluoromethyl-1H-pyrazol
 [45] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(3-methyl-4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazol
 [46] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(3-fluoro-4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazol
 [47] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(2-fluoro-4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazol;
 [48] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(2,4-dimethoxyphenyl)-3-trifluoromethyl-1H-pyrazol
 [49] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(4-fluoro-2-methoxyphenyl)-3-trifluoromethyl-1H-pyrazol
 [50] 1-(4-Aminosulphonylphenyl)-3-difluoromethyl-4,5-dihydro-5-(2,4-dimethylphenyl)-1H-pyrazol
 [51] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(2,3,4-trifluorophenyl)-3-trifluoromethyl-1H-pyrazol
 [52] 1-(4-Aminosulphonylphenyl)-5-(2-chloro-4-fluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol
 [53] 2-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(2-fluoro-4-trifluoromethylphenyl)-3-trifluoromethyl-1H-pyrazol
 [54] 1-(4-Aminosulphonylphenyl)-5-[2,4-(bistrifluoromethyl)phenyl]-4,5-dihydro-3-trifluoromethyl-1H-pyrazol
 [55] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(2-methyl-3-fluorophenyl)-3-trifluoromethyl-1H-pyrazol
 [56] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(2-methyl-4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazol
 [57] 1-(4-Aminosulphonylphenyl)-5-(2,4-difluorophenyl)-3-difluoromethyl-4,5-dihydro-1H-pyrazol
 [58] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(4-fluoro-2-trifluoromethylphenyl)-3-trifluoromethyl-1H-pyrazol
 [59] 1-(2,4-Difluorophenyl)-4,5-dihydro-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [60] 1-(4-Aminosulphonylphenyl)-5-(2-chlorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol
 [61] 1-(4-Aminosulphonylphenyl)-5-(4-chloro-2-fluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol
 [62] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(4-fluoro-2-methylphenyl)-3-trifluoromethyl-1H-pyrazol
 [63] 1-(4-Aminosulphonylphenyl)-4,5-dihydro-5-(2-fluoro-4-methylphenyl)-3-trifluoromethyl-1H-pyrazol
 [64] 1-(4-Acetylaminosulphonylphenyl)-5-(2,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol
 [65] 1-(4-Chlorophenyl)-4,5-dihydro-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [66] 4,5-Dihydro-1-phenyl-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [67] 4,5-Dihydro-1-(2-fluorophenyl)-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [68] 1-(4-Chloro-2-methylphenyl)-4,5-dihydro-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [69] 4,5-Dihydro-1-(3-fluorophenyl)-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [70] 4,5-Dihydro-1-(3-methylphenyl)-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [71] 4,5-Dihydro-1-(2,4-dimethylphenyl)-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [72] 1-(2-Chlorophenyl)-4,5-dihydro-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [73] 4,5-Dihydro-1-(2-methylphenyl)-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [74] 1-(2,4-Dichlorophenyl)-4,5-dihydro-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [75] 4,5-Dihydro-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1-(2-trifluoromethylphenyl)-1H-pyrazol
 [76] 5-(4-Aminosulphonylphenyl)-4,5-Dihydro-1-(4-fluorophenyl)-3-trifluoromethyl-1H-pyrazol
 [77] 4,5-Dihydro-1-phenyl-3-methyl-5-(4-methylsulphonylphenyl)-1H-pyrazol
 [78] 4,5-Dihydro-1-(4-fluorophenyl)-5-(4-methylsulphonylphenyl)-1H-pyrazol
 [79] (+)-1-(4-Aminosulphonylphenyl)-5-(2,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol
 [80] (-)-1-(4-Aminosulphonylphenyl)-5-(2,4-difluorophenyl)-4,5-dihydro-3-trifluoromethyl-1H-pyrazol
 [81] (+)-4,5-Dihydro-1-(4-fluorophenyl)-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [82] (-)-4,5-Dihydro-1-(4-fluorophenyl)-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [83] (+)-1-(2,4-Difluorophenyl)-4,5-dihydro-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol
 [84] (-)-1-(2,4-Difluorophenyl)-4,5-dihydro-5-(4-methylsulphonylphenyl)-3-trifluoromethyl-1H-pyrazol;

or one of their physiologically acceptable salts,

in the preparation of a medicament for preventing or treating cell proliferation diseases, particularly for preventing or treating preneoplastic or neoplastic processes, tumoral angiogenesis, cachexia and processes related to tumour necrosis factor (TNF) and, in general, those processes that can benefit from inhibition of the expression of the gene responsible for synthesising cyclooxygenase-2 (COX-2) in mammals, including man.

3. Use according to claim 1 of a compound with the general formula (I), or one of its physiologically acceptable salts, together with another product commonly used in the treatment of neoplasias, producing in this case a synergy, in the preparation of a medicament for preventing or treating cell proliferation diseases, particularly for preventing or treating preneoplastic or neoplastic processes, tumoral angiogenesis, cachexia and processes related to tumour necrosis factor (TNF) and, in general, processes that can benefit from inhibition of the expression of the gene responsible for synthesising cyclooxygenase-2 (COX-2) in mammals, including man.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/ES 02/00137

A. CLASSIFICATION OF SUBJECT MATTER IPC7 A61K 31/415, A61P 35/00, C07D 231/06 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC7 A61K, A61P, C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CIBEPAT, REGISTRY, HCAPLUS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5972986 A (SEIBERT et al.) 26.10.1999, column 9, lines 24-60; column 12, line 39 - column 13, 14, claims.	1-3
X	WO 00/76503 A (TEMPLE UNIVERSITY - OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION) 21.12.2000, table 1, page 19, line 18 - page 20, line 10.	1-3
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 7 June 2002 (07.06.2002)		Date of mailing of the international search report 28 June 2002 (28.06.2002)
Name and mailing address of the ISA/ S.P.T.O.		Authorized officer
Facsimile No.		Telephone No.

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INTERNATIONAL SEARCH REPORT
 Information on patent family members

 International Application No
PCT/ES 02/00137

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5972986 A	26.10.1999	NONE	
WO 00/ 76503 A	21.12.2000	AU 5495100 A EP 1191931 A US 6376519 B	02.01.2001 03.04.2002 23.04.2002

Form PCT/ISA/210 (patent family annex) (July 1992)